Piroxicam and Doxepin—An Alternative to Narcotic Analgesics in Managing Advanced Cancer Pain

MAJOR L. COHN, MD, PhD; ANTONIO F. MACHADO; ROBERT BIER, MD; *and* MARTHE COHN, CRNA, *Los Angeles*

To provide an effective continuum of the relief of severe carcinomatous pain with minimal side reactions, we initiated treatment with piroxicam (60 to 120 mg per day) and doxepin hydrochloride (25 to 225 mg per day). Of 30 patients presenting with severe pain of cancer of various origins, 7 continued to death with piroxicam and doxepin therapy. An additional 17 were successfully treated for 6 to 66 weeks with therapy reported here but, as disease progressed, required supplemental narcotics. The remaining six abandoned the use of piroxicam due to complications of therapy, which ranged from diarrhea to gastric perforation; serious complications were associated with patients' failure to adhere to a prescribed regimen of sucralfate. Therapy with piroxicam and doxepin proved to be safe and efficacious.

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Severe pain in patients terminally ill with cancer is managed in many countries, including the United States, almost exclusively with narcotic analgesics.[1] The justification for using these compounds relies on the belief that no other category of analgesic drug is potent enough to assuage the incapacitating pain frequently experienced by patients in advanced stages of cancer. Nonetheless, it has been reported in the United States and Great Britain that about 25% of patients with terminal cancer syndromes endure pain that is inadequately controlled,[2] and cancer pain is generally considered among the most critical of health issues facing many countries.[3] The failure to provide adequate relief stems primarily from the fact that the elevated doses of narcotics required to palliate severe carcinomatous pain commonly produce such adverse effects as anxiety, depression, confusion, insomnia, anorexia, and constipation, which greatly compound both physical discomfort and the fear of death and dying common, in varying degrees, to all patients terminally ill with cancer. In the effort to counteract the narcotic-induced side effects or enhance the alleviation of pain, or both, such widely various compounds as tranquilizers, antidepressants, hypnotics, phenothiazines, and marijuana have been proposed. Unfortunately, these drugs often intensify existing adverse effects or induce additional side reactions without significantly augmenting pain relief.

In the present investigation, we report that treatment with a nonnarcotic drug regimen consisting of the long-acting, nonsteroidal anti-inflammatory drug (NSAID) piroxicam, in combination with the tricyclic antidepressant doxepin hydrochloride, provides effective pain relief and an increased sense of overall well-being to patients referred for the management of severe pain associated with advanced stages of cancer.

Patients and Methods

The 30 patients in this study were referred to the Pain Management Center with terminal cancer syndromes and after receiving specific tumor therapies including surgical treatment, chemotherapy, and radiotherapy. Patients' ages varied from 34 to 86 years but were definitely skewed toward the fourth and fifth decades; the treatment group consisted of 14 men and 16 women, all of whom presented with malignant, histologically well-defined tumors of various causes. There was no single, predominant tumor type, but lung, colon, and breast were the most frequently represented (Table 1). Associated in each case with the advanced cancer syndrome was severe, unrelenting pain. For pain control, this patient population had been prescribed liberal doses of a minor narcotic analgesic (codeine or oxycodone) in combination with aspirin or acetaminophen. Despite extensive use of these compounds, however, all patients experienced inadequate pain control; thus, many had also been prescribed a wide variety of psychotropic drugs. As this group of patients commonly exceeded prescribed analgesic doses due to poor pain control, it was not possible to accurately record narcotic usage before this study. Patients being treated with major narcotic analgesics at the time of referral were excluded from the present trial.

At the start of investigation, a thorough medical evaluation, including a detailed history, comprehensive physical examination, complete blood chemical assessment, and review of previous medical history, radiographic films, and pathology reports, was conducted for each potential participant in an attempt to determine the origin and cause of pain and to exclude patients presenting with hemorrhagic diatheses, hematologic deficiencies, hepatic or renal failure, or a history of gastrointestinal bleeding or peptic ulcer.

Before the signing of informed consent, each patient was fully informed regarding the possibility of adverse effects associated with piroxicam and doxepin administration. Patients were encouraged to continue using narcotic analgesics if pain was inadequately controlled by the nonnarcotic therapy but were asked to carefully record dosages and sched-

From the Pain Management Center, Department of Anesthesiology (Dr Cohn, Mr Machado, and Ms Cohn), and the Department of Radiology (Dr Bier), King/Drew Medical Center, Los Angeles.

Reprint requests to Major L. Cohn, MD, PhD, King/Drew Medical Center, 1621 E 120th St, Los Angeles, CA 90059.

ules of administration. Participants were further assured that major narcotics would be made available if required.

Therapy began with a regimen of 60 mg of piroxicam per day taken in the evening 15 minutes after taking 1 gram of sucralfate. The dose of piroxicam was increased weekly by 20 mg until the patient reported being pain-free or until a maximum daily dose of 120 mg was reached. Concurrently, doxepin was prescribed to be taken on a daily basis (two to three hours before bedtime); all other psychotropic therapy was discontinued. In consultation with the Pain Management Center medical staff, patients were allowed to titrate their own daily doses of doxepin between 25 and 225 mg (mean 92.5 mg, refer to Table 1) in weekly increments of 25 mg; they were advised that the optimal dose was one that would permit sleeping through the night without causing drowsiness during the day. All drugs were administered orally.

Twice-a-week visits for medical and supportive care allowed the medical staff to adjust dosages of medication and obtain information pertaining to narcotic usage, breakthrough pain, therapeutic efficacy, and psychological state. At each visit, patients underwent laboratory tests, including a complete blood count, electrolytes, hepatic enzymes, liver and renal function, and examination of a stool specimen for occult blood. These terminally ill patients were concomitantly receiving psychiatric supportive care and, if needed, social services. Additionally, the Pain Management Center medical staff was available by telephone at all times.

Results

The causes of our patients' pain syndromes were as diverse as their tumor types (Table 1). The average survival time was 6.17 months and ranged from 2 to 16.5 months. Of the 30 patients, 7 continued to death with piroxicam and doxepin therapy; these patients required narcotics only occasionally for breakthrough pain. An additional 17 continued the therapy reported here but, as the disease progressed, required supplemental narcotics on a daily basis. The remaining six abandoned the use of piroxicam due to complications of therapy.

Patients whose pain was adequately controlled with piroxicam and doxepin uniformly reported an increased sense of overall well-being despite progression of the disease. This group of patients showed increasingly positive interactions with family, friends, and medical staff, and most gained weight. Disregarding information provided by the medical staff, five of these patients interpreted freedom from pain as remission of their disease and stopped taking their medication. Though there was no immediate reaction to this cessation, within 48 to 72 hours, pain returned with its initial intensity. As restarting the regimen of piroxicam and doxepin proved ineffective for the first day or two, these patients visited the clinic reporting that they had again begun taking narcotic analgesics because the medication "wasn't working." Only after careful questioning did we discover

TABLE 1.—*30 Patients Treated for Severe Carcinomatous Pain With a Regimen of Piroxicam and Doxepin Hydrochloride*

Patient No.	Sex	Age, yr	Site of Primary Cancer	Dose of Piroxicam, mg/day	Dose of Doxepin, mg/day	Duration of Pain Relief Without Narcotic Supplementation, wk	Complications of Therapy
1	♀	50	Lung	80	50	12	Dyspepsia
2	♀	47	Lung	80	25	11	...
3	♀	51	Cervix	100	50	16*	...
4	♀	44	Lung	100	50	20	...
5	♂	49	Colon/bladder	100	125	17	...
6	♀	50	Skin	120	150	25*	...
7	♀	48	Larynx	80	125	19	Gastrointestinal bleeding
8	♂	63	Tonsil	80	50	9*	...
9	♂	53	Colon	120	125	15*	...
10	♂	48	Nasopharynx	80	100	22*	...
11	♂	67	Multiple myeloma	60	50	47	Dizziness
12	♂	45	Lung	120	100	16	...
13	♂	47	Kidney	80	50	52	Gastric perforation
14	♂	65	Prostate	80	125	19	...
15	♂	56	Pancreas	80	100	15	...
16	♂	56	Lung	100	100	41	Gastrointestinal bleeding
17	♂	58	Tonsil	80	225	8	...
18	♀	44	Lung	80	50	21	...
19	♂	52	Lung	80	150	31	...
20	♂	51	Rectum	120	150	51	...
21	♀	86	Uterus	60	25	8*	...
22	♀	52	Lung	100	50	28	Dyspepsia
23	♀	51	Lung	60	150	16	Dyspepsia
24	♀	42	Breast	80	150	6	...
25	♀	45	Bone	80	100	66	Tinnitus
26	♀	65	Breast	80	100	7	...
27	♀	34	Cervix	100	75	12	Dyspepsia
28	♂	55	Lung	100	75	16	...
29	♀	40	Breast	80	50	13*	...
30	♀	42	Breast	60	50	5	Diarrhea

*Denotes patients who continued piroxicam and doxepin therapy without narcotics until death.

what had occurred; for these patients, piroxicam and doxepin therapy was successfully resumed.

The major side reaction due to elevated doses of piroxicam was gastrointestinal toxicity. Of the patients who consistently took sucralfate before piroxicam, none had bleeding or ulcer formation; four, however, complained of dyspepsia, an adverse effect that was alleviated when the sucralfate dosage was increased to 2 grams per day. Central nervous system side effects, such as dizziness and tinnitus, caused two of our patients to withdraw from the clinical trial; their symptoms cleared after piroxicam therapy was discontinued. We observed no cases of agranulocytosis or aplastic anemia. One patient presented with a blood platelet depression that remained unchanged when the piroxicam therapy was stopped for two weeks and restarted. Renal function and serum electrolyte values remained normal even in one patient who had undergone a nephrectomy due to adenocarcinoma. In patients who exhibited alterations in liver function, liver scans showed direct tumor involvement; no cases of hepatic dysfunction proved attributable to piroxicam and doxepin therapy. None of the patients displayed dermatologic, allergic, or ophthalmologic reactions to piroxicam.

The longest period of survival was 16.5 months. In this patient, as in all others, there was no development of tolerance or escalation of the dose of either piroxicam or doxepin. A thorough review of the cases of all patients indicated that cancer was the cause of death; in no case was there evidence suggesting a contributory effect of piroxicam and doxepin therapy.

Discussion

Once therapeutic procedures intended to control tumors have been exhausted, it is generally agreed upon that pain control is a principal objective in the treatment of patients presenting with advanced forms of cancer. Narcotic analgesics have been the primary compounds used in the pharmacologic attempt to alleviate severe carcinomatous pain.[1] Because alternate drug therapies are, in general, considered inadequately effective, opiate analgesics have been used despite their patently negative impact on patients' well-being. Although for this preliminary investigation we were unable to "objectively" measure the quality of life, our patients without exception reported an increased sense of overall well-being and, in most cases, excellent pain palliation. Thus, what have been termed "key" components[4] of increasing the quality of life in terminally ill patients—preventing or alleviating physical and psychological stress, maintaining physical and mental functioning, and controlling pain—have been fulfilled to the best of our estimation.

Some of the improved sense of well-being uniformly reported by these patients suffering from severe pain associated with advanced stages of cancer was undoubtedly due to the therapeutic inclusion of the tricyclic antidepressant, doxepin. Even small doses of doxepin effectively palliated symptoms such as insomnia, fatigue, and depression. In addition, there is general agreement[5-7] that the use of tricyclic antidepressants in managing pain does not require elevated doses; nonetheless, the question of whether these compounds directly affect pain perception remains controversial.[8]

Compared with narcotic analgesics, the primary advantages of therapy with piroxicam and doxepin are that these compounds are neither addictive nor associated with tolerance, respiratory depression, psychotropic disturbances, central nervous system depression, or anorexia. Piroxicam was selected as the NSAID in this investigation due to its long plasma half-life,[9] which allowed the administration of this compound once per day with effectiveness. This is an important factor as, in our observation, failure to obtain a continuum of pain control with shorter acting NSAIDs is a major rationale for discontinuing NSAID therapies. In addition, a single daily administration of medications is far more conducive to patients' compliance than a regimen requiring the administration of one or more analgesics several times per day.[9]

Past experience (unpublished observations) indicated 60 mg per day as the appropriate starting dose for piroxicam; most patients with pain from advanced forms of cancer, however, required 80 mg per day and some as high as 120 mg per day (Table 1). Patients uniformly reported an analgesic effect 48 to 72 hours subsequent to the initiation of therapy; this lag period is characteristic of piroxicam.[9] In agreement with reports that, despite its long plasma half-life, piroxicam's low drug burden prevents accumulation of this compound,[9,10] no cumulative effects of piroxicam were observed in this trial, and frequent laboratory tests and thorough medical reviews of all patients greatly reduced the degree of risk. Three of our patients took it upon themselves to divide the dose of piroxicam in the manner they were accustomed to taking other NSAIDs. These patients, as they lacked sufficient sucralfate for multiple administrations of piroxicam, had the rapid development of signs of gastrointestinal distress. Within two weeks, two of these patients suffered gastrointestinal hemorrhaging and had to discontinue therapy. A fourth patient who failed to take sucralfate before piroxicam required surgical repair of a silent perforation of a gastric ulcer.

All current modalities of analgesic drug therapy require the striking of a judicious balance between pain relief effectiveness and toxic side effects. All NSAIDs are associated with a potential for gastrointestinal ulceration, perforation, and bleeding; one responsible mechanism is the inhibitory effect NSAIDs exert on prostaglandin synthesis.[11] Specifically, NSAIDs, including piroxicam, inhibit arachidonic acid from converting to prostaglandin endoperoxide, thus reducing cytoprotection of the upper gastrointestinal tract. The toxic actions of piroxicam on various systems have been comprehensively reported.[12,13]

At the start of this clinical trial, the Pain Management Center medical staff was aware that an inability to prevent gastrointestinal toxicity would lead to the failure of piroxicam and doxepin therapy. The well-known anticholinergic effect of doxepin has been shown to reduce gastrointestinal stress by decreasing total gastric acid secretion,[14] but this effect alone does not provide full protection. In previous trials with this therapy, we prescribed cimetidine to prevent gastrointestinal upset; in our experience, however, this drug proved inadequately protective, an observation that correlates with subsequently published reports that cimetidine is ineffective in cases of nonulcer dyspepsia.[15] Thus, we prescribed sucralfate, which prevented peptic toxicity except in the four cases previously referred to wherein the patients admitted to disregarding our instructions concerning its use. The effectiveness of this compound in averting gastrointestinal complications is in agreement with reports that sucralfate provides both short-term and long-term protection to patients on a continued regimen of NSAIDs.[16] The recently introduced prostaglandin

endoperoxide analogue, misoprostol, may serve even better in preventing gastrointestinal toxicity.

It is interesting to note that NSAIDs are not as "mild" analgesics as they are often termed. In comparing the efficaciousness of aspirin and morphine for postsurgical pain, the two compounds were found to provide equally effective relief.[17] Moreover, NSAIDs have been reported to control severe pain "in many situations," including cases of pain associated with cancer.[18] The daily dosage of piroxicam required by our group of patients was as much as six times the suggested dose of 20 mg a day; the suggested dose, however, is based on anti-inflammatory activity using arthritic models.[19-22] In our observation, the control of severe pain of a malignant origin requires a minimum of 40 mg per day and, more commonly, 60 to 100 mg per day. Establishing effective analgesic activity requires two to four days, a latency of onset that may be attributed to extensive serum protein binding[9]; consequently, piroxicam should always be administered on a scheduled basis, never only as needed. Dosages should be gradually increased until the desired level of analgesia is reached or until adverse side reactions develop. Our observations indicate that, for most patients, 120 mg per day is the maximum dose that may be safely tolerated in combination with doxepin and an adequate course of sucralfate.

While mild hepatic dysfunction and, in rare cases, severe hepatitis have been associated with administering piroxicam,[16] we observed no hepatitis, cholangitic jaundice, or alterations in hepatic enzymes. As renal activity plays a limited role in the metabolic elimination of piroxicam,[23] renal toxicity due to this compound is rarely reported in patients with normal kidney function,[24] and, in the present trial, piroxicam administration resulted in no nephrotoxicity. Because of its inhibitory effect on prostaglandin synthesis, piroxicam may cause fluid retention and decreased sodium excretion.[10] Although no such effect occurred in the patients in this study, careful evaluation is indicated.

Because NSAIDs suppress fever, disease states characterized by a febrile reaction may go undetected in patients taking piroxicam on a long-term basis. Again, this clinical observation serves to stress the importance of systematic follow-up for patients on a piroxicam and doxepin regimen. All NSAIDs exhibit, as well, the potential to interfere with platelet function or cause agranulocytosis or aplastic anemias. Although blood dyscrasias were noticeably absent in the present group of patients, we may expect, in a larger sampling of subjects, such toxic effects to occur. For that reason and the fact that difficulties may arise in distinguishing between adverse effects elicited by piroxicam and symptoms due to progressing cancer syndromes, patients prescribed piroxicam and doxepin therapy for severe carcinomatous pain should be observed with extreme caution, and, of course, piroxicam should not be administered concomitantly with chemotherapy. Frequent blood and stool assessments are a necessary safeguard against occult toxicity.

In assessing the applicability of piroxicam and doxepin therapy, we note that effective pain relief was achieved despite the diversity of tumor types, resulting in widely various pain origins in this patient population; it is also interesting that the therapy proved equally effective for pain arising from visceral and bony sources. In accordance with the World Health Organization's guidelines for the management of carcinomatous pain, patients should be treated with nonnarcotic analgesics for as long as effective pain relief may be maintained with relative safety. It has been reported, however, that in most patients the time period of management with narcotics is "more than twice as long" as that of nonnarcotic management, which is generally "less than three weeks."[25] The present study would seem to indicate the possibility of reversing that time frame in many patients.

Overall, piroxicam and doxepin therapy for extreme pain due to various terminal cancer syndromes has proved, in this limited trial, to be an efficacious and beneficial alternative to management with narcotic analgesics regardless of the severity, duration, or origin of pain. The therapy may prove particularly useful in patients who do not respond well to narcotic analgesics.

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